

REMARKS

Claims 31 and 32 have been amended. Amended claims 31 and 32 are supported by the specification and the original claims, for example, original claim 1; original claim 2.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments and the following remarks is requested.

I. The Rejection of Claim 32 under 35 U.S.C. 112 (Indefiniteness)

Claim 32 is rejected under 35 U.S.C. 112, paragraph 2, as being indefinite. The Examiner states that it is unclear how the variant of claim 32, which requires a mutation in amino acid 153 of SEQ ID NO:2 is within the scope of claim 31, which *only* allows mutations in regions 98-110 and 161-167. See July 08, 2005 Office Action at page 2 (emphasis added). This rejection is respectfully traversed.

Claim 31 **does not** "only allow" mutations in regions 98-110 and 161-167 of SEQ ID NO:12, as the Examiner states. Rather, claim 31 is directed to "a variant of a parent Fungamyl-like alpha-amylase, *comprising* an alteration at one or more regions selected from the group consisting of region 98-110 and region 161-167." (emphasis added.) Use of the transitional term "comprising" in a patent claim indicates that the claim is open-ended. See, for example, *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997) ("comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim."); see also *Regents of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1573 (Fed. Cir. 1997) ("the word 'comprising,' . . . as is well-established permits inclusion of other moieties.") Thus, it is respectfully submitted that claim 32, which depends from claim 31 and claims variants of claim 31 that additionally also comprise the mutation Q153S, is within the scope of claim 31. In order to clarify the scope of the present invention, claim 32 has been amended as indicated above.

For the foregoing reasons, Applicants submit that this rejection under 35 U.S.C. 112 is improper. Applicants respectfully request reconsideration and withdrawal of the rejection.

II. The Rejection of Claims 31-48 under 35 U.S.C. 112 (Indefiniteness)

Claims 31-48 are rejected under 35 U.S.C. 112, paragraph 2, as being indefinite. The Examiner states that the phrase in claim 31 "each region or position corresponds to a region position of the amino acid sequence of the parent.." is unclear. See Office Action mailed July 08,

2005 at page 2. The Examiner further states that it is unclear why the term "region" in line 2 of claim 31 starts with a capital letter whereas the term "region" in line 7 does not. See July 08, 2005 Office Action at pages 2-3.

Claim 31 has been amended to correct a typographical error regarding the omission of the term "or" in the phrase cited above. Thus this issue is now moot. The term "region" in line 2 of claim 31 is capitalized because the term "region" as used in that line refers to the specific regions of SEQ ID NO:2 between amino acids 98-110 and between amino acids 161-167, respectively. The term "region" in line of claim 31 is not capitalized because the term "region" as used in that line refers to regions or positions of variants that correspond to Region 98-110 or Region 161-167 of SEQ ID NO:2. In order to expedite prosecution, however, claim 31 has been amended so that the term "region" in line 2 now starts with a lower-case "r".

Applicants respectfully request withdrawal of the rejection, as the issues raised by the Examiner are now moot.

III. The Rejection of Claims 42-46 under 35 U.S.C. 112 (Enablement)

Claims 42-46 are rejected under 35 U.S.C. 112, paragraph 1, as lacking enablement. The Examiner states that the specification, while enabling for variants of SEQ ID NO:2 having at least 97% identity to SEQ ID NO:2 with amylase activity, does not reasonably provide enablement for variants of SEQ ID NO:2 having at least 70%-95% identity to said amino acid sequence while retaining fungamyl-like alpha-amylase activity. See July 08, 2005 Office Action at page 3. The Examiner further states that the specification fails to teach which amino acid residues beyond those in regions 98-110 and 161-167 of SEQ ID NO:2 must be retained in the claimed homolog of SEQ ID NO:2 such that said homologs retain alpha-amylase activity. See July 08, 2005 Office Action at page 4. This rejection is respectfully traversed.

The rejection is concerned with whether an artisan would be able to practice the claimed invention without undue experimentation. The claims are directed to variants of the alpha amylase of SEQ ID NO:2 that have a high degree of homology with SEQ ID NO:2. See specification at page 10, lines 4-26. The homology of a variant alpha amylase to SEQ ID NO:2 to the amino acid sequence of SEQ ID NO:2 may be determined, for example, by means of computer programs known in the art, such as GAP provided in the GCG program package. Id. GAP uses methods well known in the art to make alignments and to calculate the identity between two protein or DNA sequences. See specification at page 10, lines 17-19. There is an extensive body of patent and scientific literature relating to alpha amylases, see specification at page 1, lines

24-25. Fungamyl™-like alpha amylases, including the alpha amylase of SEQ ID NO:2, are also well known in the art, as disclosed, for example, in EP 238 023; see also specification at page 5, lines 31-35, and the three-dimensional structure of the alpha amylase of SEQ ID NO:2 is well-known. See specification at page 5, lines 11-26. The specification describes many alpha amylases falling within the claimed invention that an artisan can use to practice the claimed invention. See specification at page 7, line 26-page 9, line 3.

The specification also provides detailed guidance for identifying suitable amino acid residues for modification on variants of SEQ ID NO:2. As noted supra, the three-dimensional structure of the alpha amylase of SEQ ID NO:2 is well-known. See specification at page 5, lines 11-26. This structure is a useful tool for an artisan to determine which additional amino acids can be altered and which amino acids should be conserved to practice the claimed invention. See specification at page 2, line 34-page 3, line 32. The identification of specific positions or regions to be mutated on variants of SEQ ID NO:2 in order to obtain improved thermostability may be achieved, for example, by using molecular dynamics simulations to find regions having the highest mobility or flexibility. See specification at page 2, line 34-page 3, line 32. Substitutions may be directed against residues in these regions. See specification at page 3, lines 6-13. The specification further describes processes of producing alpha-amylase variants related to SEQ ID NO:2 that fall within the claimed invention by, for example, site-directed mutagenesis, see specification at page 13, line 11-page 14, line 1, and localized or region-specific random mutagenesis, see specification at page 14, line 4-page 17, line 25; specification at page 17, line 27-page 18, line 14. It would thus be routine for the skilled artisan to make the claimed variants commensurate with the scope of the invention.

Thus, it is submitted that the claims are enabled. For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

IV. The Rejection of Claims 42-46 under 35 U.S.C. 112 (Written Description)

Claims 42-46 are rejected under 35 U.S.C. 112, paragraph 1, as failing to meet the written description requirement. The Examiner states that the claims contain subject matter that was not described in the specification in a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. See July 08, 2005 Office Action at page 4. The Examiner further states that claims 42-46 are directed to a genus of alpha-amylase homologs that have been inadequately described in the

specification. July 08, 2005 Office Action at pages 4-5. The Examiner further states that the specification discloses only a single species (SEQ ID NO:2 with allowed mutations in regions 98-110 and 161-167) of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. July 08, 2005 Office Action at page 5. The Examiner also states that the specification does not contain any disclosure of the structure of *all* alpha-amylase homolog sequences that are 70-95% identical to SEQ ID NO:2. July 08, 2005 Office Action at page 5 (emphasis added). This rejection is respectfully traversed.

The Federal Circuit recently discussed the written description requirement in the context of biological subject matter in *Capon v. Esshar*, 418 F.3d 1349 (Fed. Cir. 2005), stating that "the determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter." *Id.* at ____ [publication page not available].

The Federal Circuit specifically noted that "it is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention." *Capon v. Esshar*, 418 F.3d at ____.

As noted supra, alpha amylases are well known in the art. There is an extensive body of patent and scientific literature relating to alpha amylases. See specification at page 1, lines 24-25. Fungamyl™-like alpha amylases, including the alpha amylase of SEQ ID NO:2, are also well known in the art, as disclosed, for example, in EP 238 023; see also specification at page 5, lines 31-35, and the three-dimensional structure of the alpha amylase of SEQ ID NO:2 is likewise well-known. See specification at page 5, lines 11-26.

The specification describes many alpha amylase variants falling within the claimed invention that an artisan can use to practice the claimed invention using the amino acid backbone of SEQ ID NO:2. See specification at page 6, line 26-page 9, line 2. The specification also provides detailed guidance for identifying other alterations that can be made, using, for example the three-dimensional structure of SEQ ID NO:2 and molecular dynamics simulations, to identify suitable amino acids for modification in variants of SEQ ID NO:2. See specification at page 2, line 34-page 3, line 32. Applicants therefore submit that specification provides sufficient support for alpha amylase variants having at least 70%, 80%, 90%, 93%, 95% identity to SEQ ID NO:2 within the scope of the claims, and that it is not necessary to disclose the structure of all variants

that fall within the claimed invention to demonstrate that Applicants were in possession of the invention at the time the application was filed. See *Capon v. Esshar*.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

V. The Rejection of Claims 31-48 for Double Patenting

Claims 31-48 are provisionally rejected under the judicially created doctrine of double patenting over claims 31-33, 39-43, 50-62 of co-pending Application No. 09/710,339. Applicants note that a terminal disclaimer has been filed. Therefore, Applicants submit that this rejection is now moot.

Applicants respectfully request withdrawal of the rejection.

VI. The Rejection of Claims 31-48 under 35 U.S.C. 103

Claims 31-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Christianson in view of Matsuura further in view of Svendsen. The Examiner contends that Christianson et al. teach (1) identifying amino acid sites in a target protein which has an effect on stability of the target protein by imputing the three dimensional coordinates into a computer, (2) generating a probe-accessible surface of the target protein, (3) identifying amino acids which make boundaries of internal cavities which have an effect on the stability of the protein, (4) mutating at least one of the sites to create a mutant target protein, and (5) expressing and isolating the mutant target protein. The Examiner states that Christianson does not disclose the alpha-amylases of the present invention as target proteins. However, the Examiner contends that Matsuura et al. disclose an amino acid sequence matching SEQ ID NO:2 of the present invention. Although neither Christianson et al. nor Matsuura et al. teach the specific alterations recited in the present claims, the Examiner contends that Svendsen et al. guides an artisan to find regions where the structure of the alpha-amylase can be mutated in order to obtain a more stable or heat resistant variant. The Examiner states that Svendsen et al. teaches that all alpha-amylase have a few conserved regions with approximately the same length and spacing and that certain alterations taught by Svendsen et al. are equivalent to alterations recited in the present claims.

This rejection is respectfully traversed. None of the cited reference teach or suggest the variant fungal-related alpha-amylases recited in the present claims. Christianson is directed to bacterial protease enzyme and methods for producing same. Matsuura et al. discloses fungal alpha-amylases, but does not teach or suggest the alterations recited in the present claims.

Svendsen et al. is directed to bacterial-related alpha-amylase variants. The Examiner contends that Svendsen et al. teaches that all alpha-amylase have conserved regions, and that the alterations in Svendsen et al. are equivalent to the alterations in the fungal-related alpha-amylase variants of the present invention. However, the alterations of Svendsen et al. are based on the aspects of bacterial-related alpha-amylases, i.e., Termamyl-like alpha-amylases, which have very low homology and extremely low identity to the fungal related alpha-amylases of the present invention. Indeed, although Svendsen et al. teaches that there is some conservation between the bacterial and fungal alpha-amylases, Svendsen et al. specifically states that the variants it describes are "based on some striking, and not previously predicted difference between" the Termamyl-like alpha-amylase structure and both fungal and mammalian alpha-amylase. See Svendsen et al. at page 3, lines 6-18. Therefore, Svendsen et al., alone or in combination with Christianson et al. and Matsuura et al., clearly does not suggest the alterations in fungal-related alpha-amylases, as claimed in the present invention.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 103. Applicants respectfully request reconsideration and withdrawal of the rejection.

VII. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,



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